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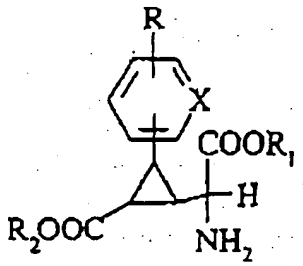
(54) Title: GLYCINE DERIVATIVES

(57) Abstract

Compounds of formula (I), wherein R, R_1, R_2 and X are as defined in the description, are useful as pharmaceuticals.



(I)

GLYCINE DERIVATIVES

The present invention relates to glycine derivatives with affinity to metabotropic glutamate receptors.

Metabotropic glutamate receptors (mGluR) are a family of proteins present in neurons and in the glia, which can interact with glutamate and bring about significant modifications in neurotransmission by interaction with protein G and the resulting regulation of the neosynthesis of second messengers or the modulation of ion channels both at the presynaptic and postsynaptic levels. Recent molecular biology studies have identified at least eight cDNAs which likewise code for mGluR subtypes. In general, on the basis of structural analogies, the effector used and pharmacological properties, it is possible to divide the eight mGluRs into three groups:

1st group: comprises mGluR1 and mGluR5 which are capable of stimulating phospholipase C and the inositol cycle. These receptors are stimulated by the antagonists in the following order of power: QUIS> 1S, 3R-ACPD>L-CCG1>>>>L-AP4.

2nd group: comprises mGluR2 and mGluR3 which are capable of inhibiting the formation of cAMP induced by forskolin. The order of power of the agonists is as follows: L-CCG1>1S,3R-ACPD>QUIS>>>>>L-AP4.

3rd group: comprises mGluR4, mGluR6, mGluR7 and mGluR8 which are also capable of inhibiting the formation of cAMP, but in the following order of power:L-AP4>>1S,3R-ACPD>>>>L-CCG1.

The various mGluRs are differentially distributed in the CNS and several subtypes may coexist in the same area and also in the same neuron. The final effect their activation has depends on the types of receptor present and may therefore be either an inhibitory effect or an

excitatory effect. For example, in the cerebellum, the stimulation of mGluR1 leads to activation of the calcium-dependent potassium channels and therefore to inhibition, whereas, in the hippocampus, activation of mGluR receptors can increase the neuronal excitability by inhibiting the voltage-operated potassium channels. Then there are mGluRs which are localized to the presynaptic level and are capable of regulating the release of the transmitter by means of particularly interesting mechanisms. Thus, the stimulation of mGluR4 or mGluR7 can reduce the influx of Ca^{2+} into the nerve endings, thereby directly inhibiting the voltage-dependent channels and reducing the synaptic release of transmitter. A similar result can be obtained by stimulating the mGluR2 or mGluR3 receptors, which inhibit the formation of cAMP and in some way reducing the effects of depolarization on the release of the transmitter. In contrast, the stimulation of other mGluR subtypes (mGluR1 and possibly also mGluR5) amplifies the depolarization-release of transmitter combination, especially in the presence of free fatty acids.

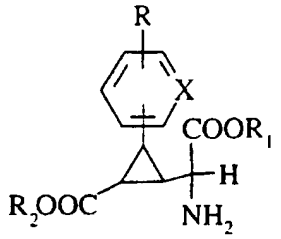
In light of the above, regulation of the functioning of mGluR-controlled neuronal circuits in the hippocampus becomes particularly advantageous. Stimulation of the mGluR4 and mGluR7 receptors reduces transmission at the glutamatergic synapses level, whereas stimulation of mGluR5 can increase the excitability of the circuit, possibly also because it amplifies responses of ionotropic type. The consequences of a reduction in transmission and an increase in excitability are that low-intensity stimuli are blocked, while strong stimuli, capable of overcoming the presynaptic inhibition, are amplified. In this way, the strategic location of the mGluRs leads to the formation of filtering systems capable of increasing the signal/noise ratio of the stimuli which converge on this neuronal circuit. Such systems, in which other types of mGluR also come into play, appear to operate both at the level of phenomena associated with learning and in regulating various

sensory signals (for example in the olfactory pathways). In the basal nuclei, the stimulation of mGluR2 and mGluR3 leads to a considerabl reduction in the synaptic release of excitatory transmitter and may affect certain psychic and motor functions. Thus, the pharmacology of mGluRs appears to promise wide fields of therapeutic application since mGluRs appear to have an important role in the processes of neuroprotection and neurodegeneration, in controlling movement, and in the normal functioning of dopaminergic systems, in the onset of epileptic attacks, in the processes of central integration of pain, pressure, visual and sensory stimuli, and in learning. The fact that stimulation of the mGluR receptors can bring about an increase in the sensitivity of the ionotropic receptors for the same transmitter makes these receptors an ideal target for modifying synaptic excitatory functioning.

WO 93/08158 (Suntory Ltd.; 29.4.1993) describes enantiomers of 2-(2,3-dicarboxycyclopropyl)glycine as NMDA-receptor agonists and their therapeutic use as anaesthetics, analgesics and antispastic agents.

It has now been found that cyclopropylglycine derivatives are endowed with affinity to metabotropic glutamate receptors.

The compounds of the invention have the general formula (I) below



(I)

in which

R is hydrogen, halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, cyano, nitro, $-COOR_1$ (R_1 being as defined below), $-CONR_3R_4$ (R_3 and R_4 independently being hydrogen or C_1-C_4alkyl), $-PO(OR_1)_2$ (R_1 being as defined below), $-SO_3R_1$ (R_1 being as defined below) or $-NH-CO-R_5$ (R_5 being C_1-C_4alkyl or phenyl),

R_1 and R_2, independently, are hydrogen, C_1-C_4alkyl or benzyl, and

X is =CH-, =N- or $=N^+(O^-)-$

The compounds of formula (I) have four asymmetric centres, which give rise to 16 enantiomers.

The invention comprises the individual enantiomeric forms as well as their racemic or diastereoisomeric mixtures.

The invention moreover comprises the salts of the compounds (I) with acids or (when R_1 or R_2 = H) bases.

In a group of compounds of formula I, R is hydrogen, an halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl or C_1-C_4haloalkoxy, R_1 and R_2 are hydrogen and X is =CH- or =N- in ortho position to the bond which is linked to the cyclopropyl moiety.

Preferred compounds of formula (I) are those in which X is CH and R is hydrogen or a C_1-C_4 alkoxy group.

Examples of C_1-C_4 alkyl groups include methyl, ethyl, n-propyl, isopropyl and isobutyl, preferably methyl.

Examples of C_1-C_4 alkoxy groups include methoxy, ethoxy, n-propoxy and isopropoxy, preferably methoxy.

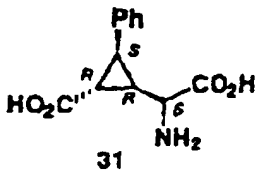
Examples of C_1-C_4 haloalkyl groups include trifluoromethyl and pentafluoroethyl, preferably trifluoromethyl.

Examples of C_1-C_4 haloalkoxy groups include trifluoromethoxy and difluoromethoxy, preferably tri-

fluoromethoxy.

Th formulae of 16 possible enantiomers of the compounds of formula (I) in which R is H, X is =CH- and R_1 is hydrogen are given below. The S configuration of the carbon atom of the glycine residue is preferred and the configuration of compound 44 is particularly preferred.

S Series



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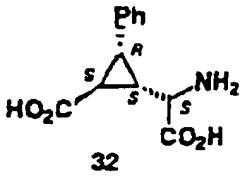

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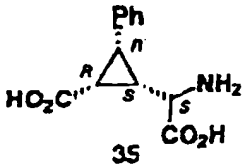

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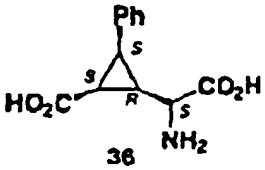

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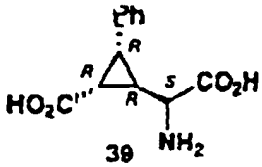

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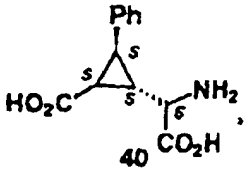

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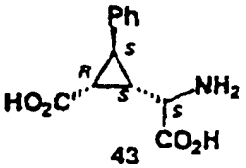

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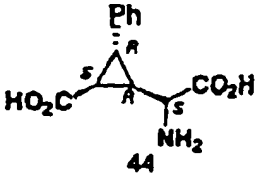

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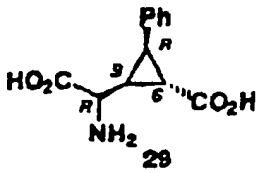
R Series



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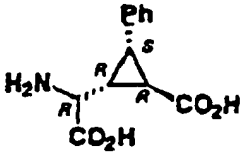

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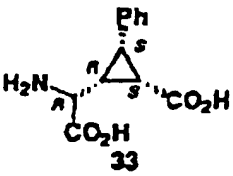

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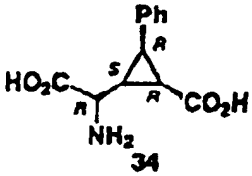

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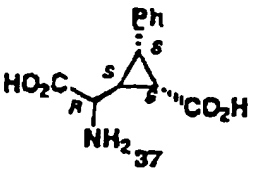

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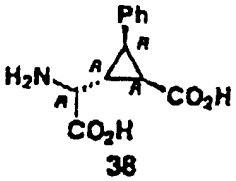

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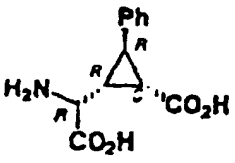

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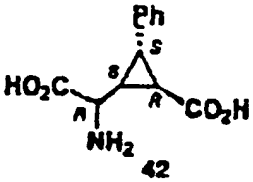

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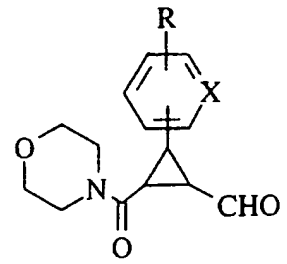
The compounds of formula I wherein R_1 and R_2 are H may be prepared by reaction of a compound of formula (II)



(II)

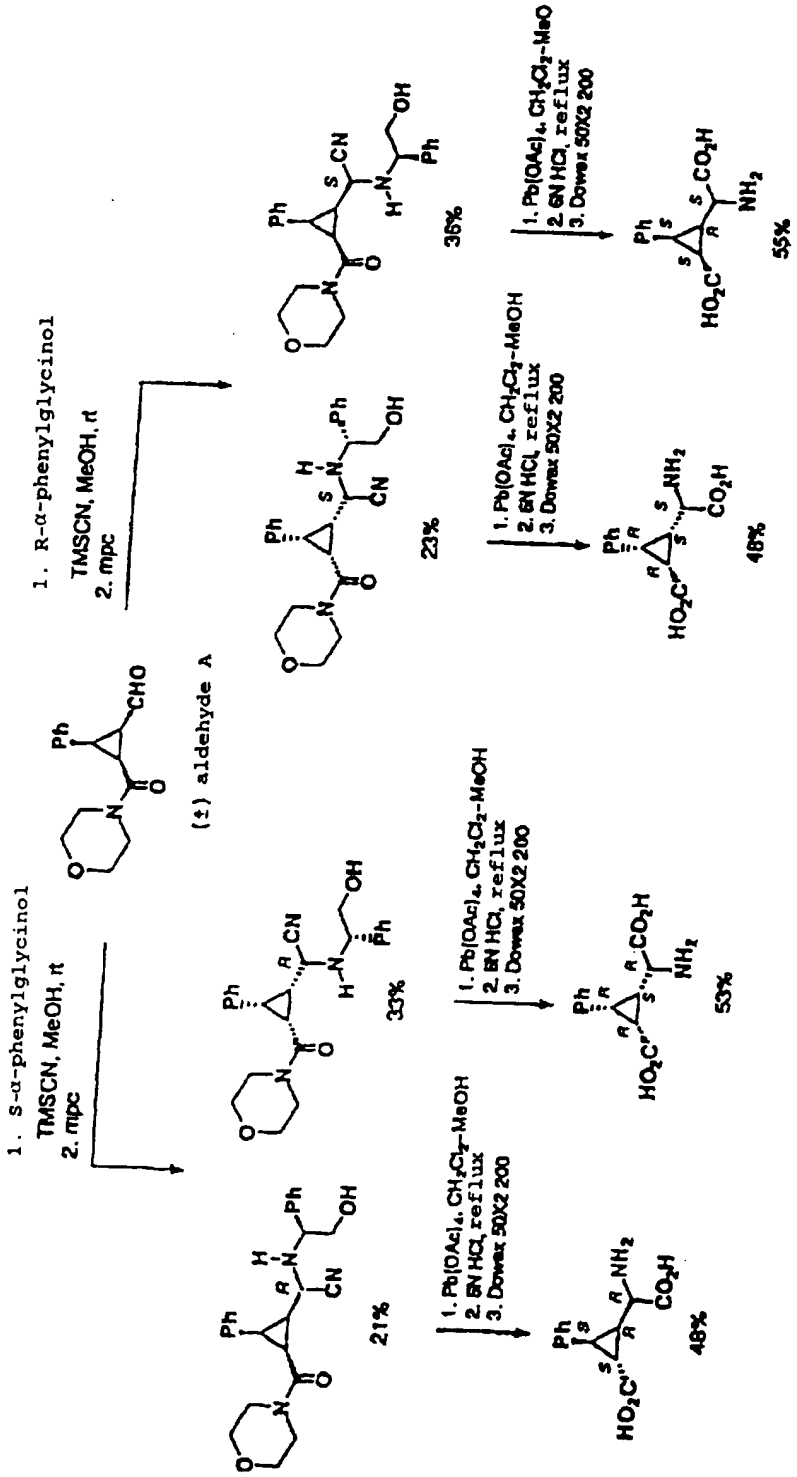
in which X and R are as defined above, with α-phenylglycinol and then with TMSCN, followed by oxidative cleavage with lead tetraacetate and acid hydrolysis. The compounds wherein R_1 and/or R_2 are alkyl or benzyl can be prepared from the free acids according to well known procedures.

By using various enantiomers of the aldehydes (II) and of R- or S-α-phenylglycinol, the desired enantiomers may be prepared.

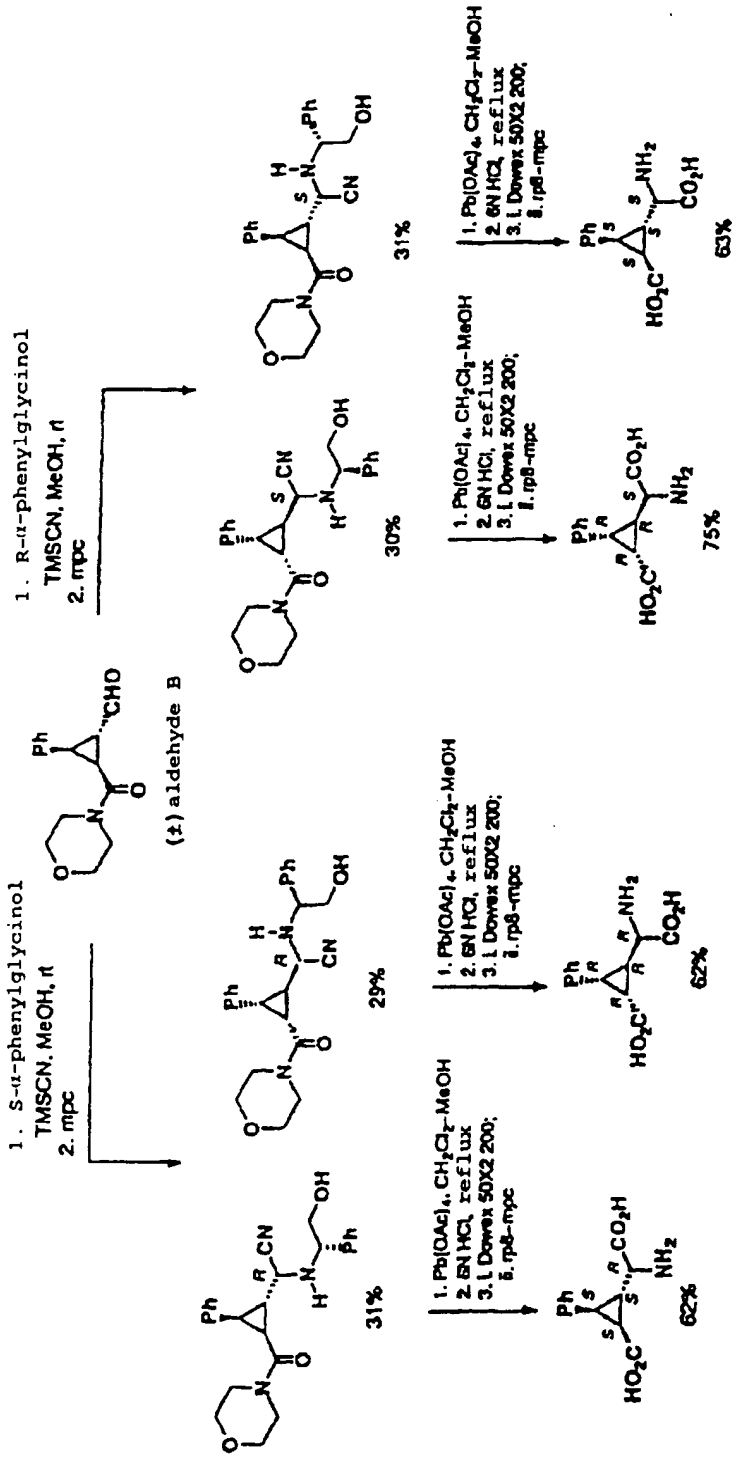
Schemes 1-4 for the preparation of compounds (I) in which X = CH and R = H are given below. Further compounds (I) can be obtained by identical methods, starting with appropriate aldehydes (II).

Aldehydes (II) can be prepared according to the following schemes 5 and 6, again with reference to compounds in which X is CH and R is hydrogen. Obviously, further aldehydes of formula (II) can be prepared in a similar manner, starting with the appropriate E-cinnamyl or E-pyridylvinyl alcohols.

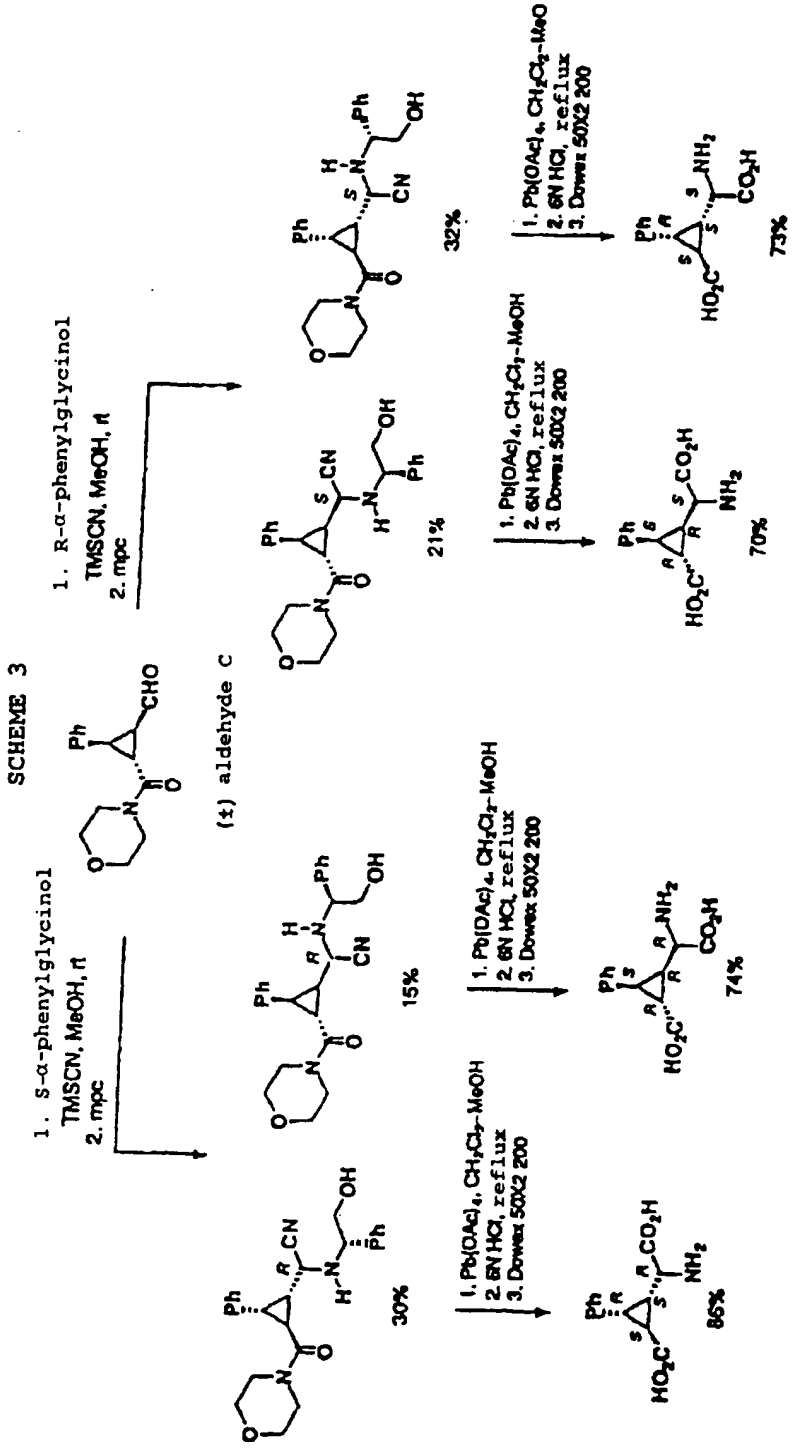
SCHEME 1


1. S-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
(±) aldehyde A
1. R-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
21%
33%
23%
36%
1. Pb(OAc)4, CH2Cl2-MeOH
2. 6N HCl, reflux
3. Dowex 50X2 200
48%
53%
48%
55%

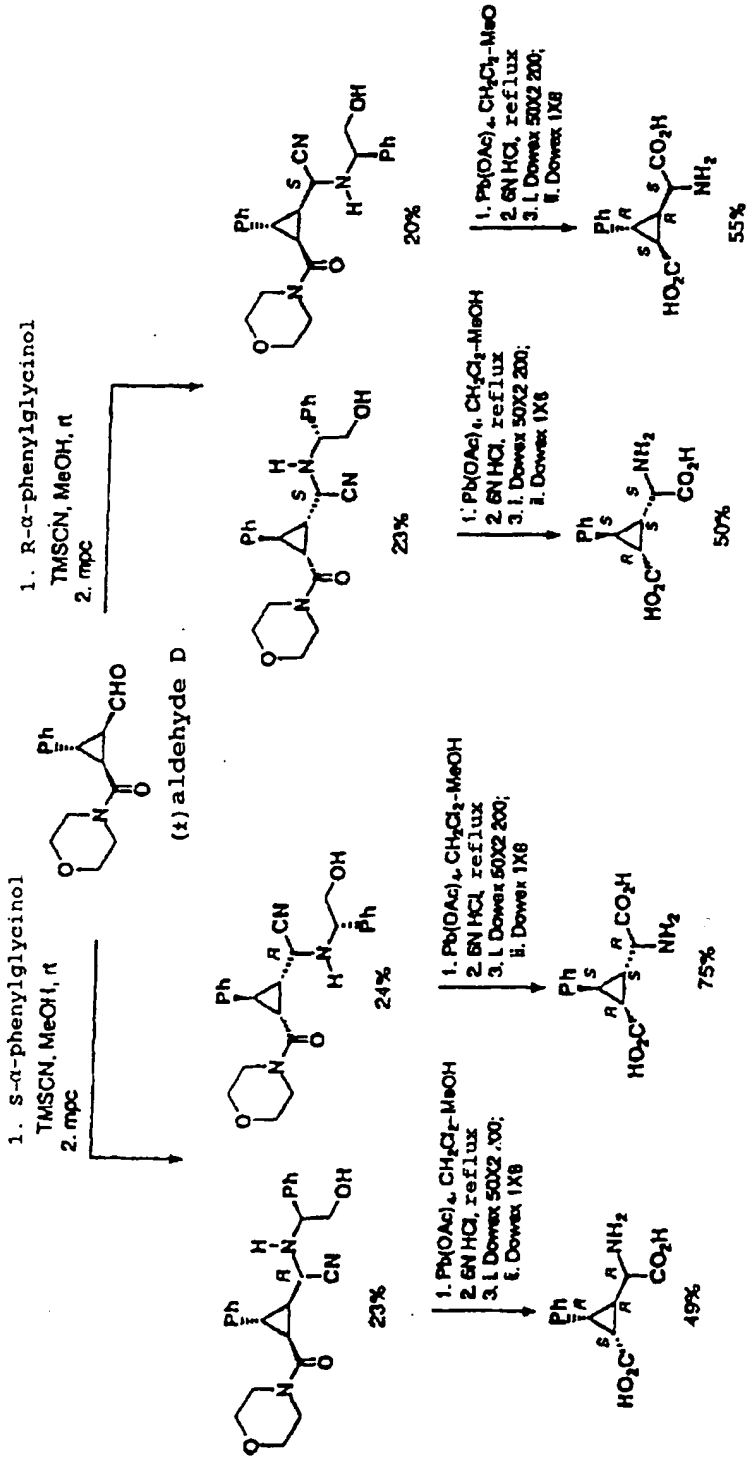
SCHEME 2


1. S-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
(±) aldehyde B
1. R-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
31%
29%
30%
31%
1. Pb(OAc)4, CH2Cl2-MeOH
2. 6N HCl, reflux
3. 1. Dowex 50X2 200;
ii. rp8-mpc
62%
62%
75%
63%

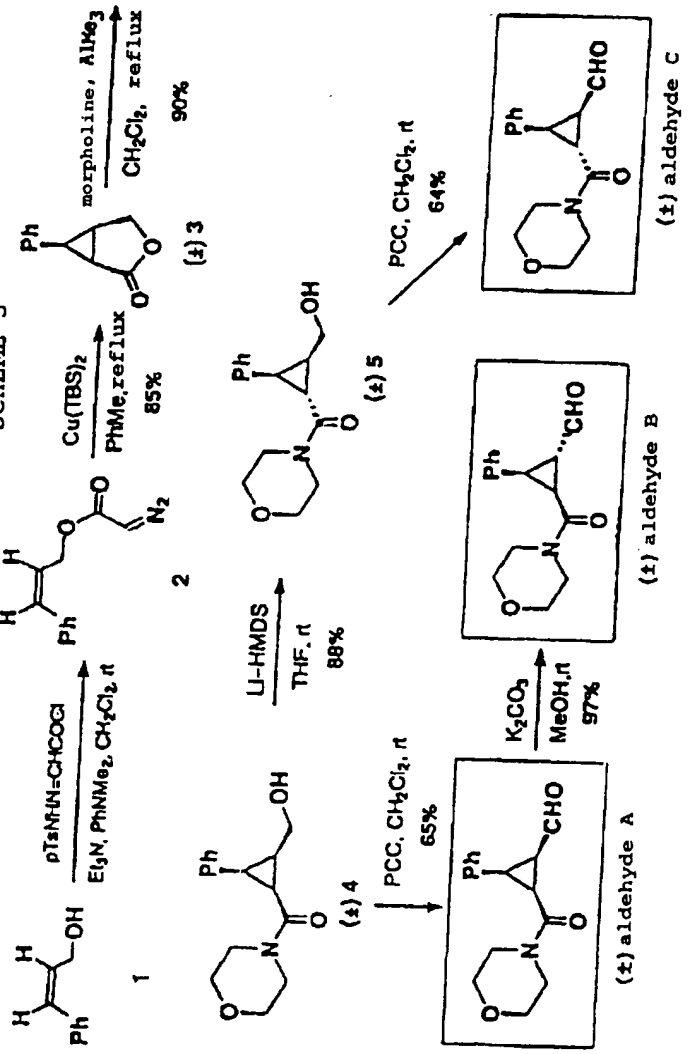
SCHEME 3


1. S-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
(±) aldehyde C
1. R-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
30%
15%
21%
32%
1. Pb(OAc)4, CH2Cl2-MeOH
2. 6N HCl, reflux
3. Dowex 50X2 200
74%
70%
73%
86%

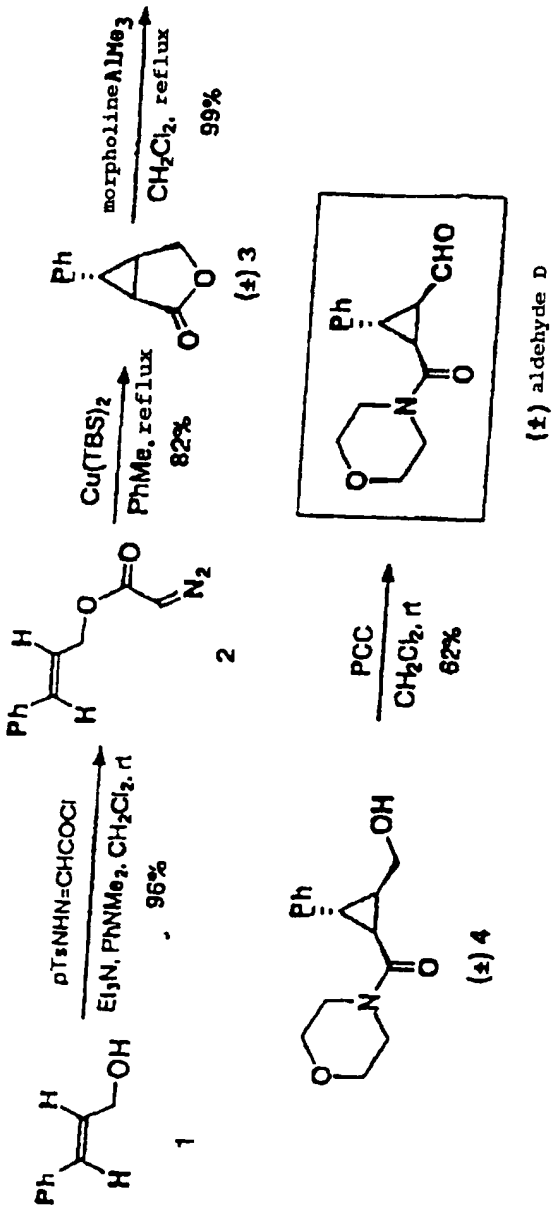
SCHEME 4


1. S-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
(±)aldehyde D
1. R-α-phenylglycinol
TMSCN, MeOH, rt
2. mpc
24%
23%
20%
23%
1. Pb(OAc)4, CH2Cl2-MeOH
2. 6N HCl, reflux
3. i. Dowex 50X2 200;
ii. Dowex 1X8
75%
49%
50%
55%

SCHEME 5


pTsN=N-CHOCl
Et3N, PhNMe2, CH2Cl2, rt
Cu(TBS)2
PhMe, reflux
85%
morpholine, AlMe3
CH2Cl2, reflux
90%
Li-HMDS
THF, rt
88%
PCC, CH2Cl2, rt
65%
PCC, CH2Cl2, rt
64%
K2CO3
MeOH, rt
97%
(±) aldehyde A
(±) aldehyde B
(±) aldehyde C
Cu(TBS)2 =
bis(N-t-Bu-salicylaldiminato)copper (II)
[E.J. Corey, et al., Tetrahedron Lett. 1984, 25, 3559]

SCHEME 6


pTsNHN=CHCOCl
Et3N, PhNMe2, CH2Cl2, rt
96%
Cu(TBS)2
PhMe, reflux
82%
morpholineAlMe3
CH2Cl2, reflux
99%
PCC
CH2Cl2, rt
62%
Ph
OH
CHO
N
O
1
2
(±) 3
(±) 4
(±) aldehyde D

The compounds of formula (I) and their pharmaceutically acceptable salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro, particularly affinity to metabotropic glutamate receptors (mGluRs) as indicated above, and are therefore useful as pharmaceuticals.

The agents of the invention were evaluated as mGluR antagonists in the following tests:

1) Antagonism of the phospholipase C-stimulatory action by 1S,3R-ACPD (300 µM) on slices of rat cortex. Active molecules in this test are considered to be mGluR1 or mGluR5 antagonists (group 1).

2) Antagonism of the action of L-CCG1 (3 µM) on the formation of cAMP induced by forskolin (30 µM) on slices of rat stria. Active molecules in this test are considered to be mGluR2 or mGluR3 antagonists (group 2).

3) Antagonism of the action of L-AP4 (10 µM) on the formation of cAMP induced by forskolin (30 µM) on slices of rat cerebellum. Active molecules in this test are considered to be mGluR4, mGluR7 and mGluR8 antagonists (group 3).

The agents of the invention show significant activity in these tests at about 0.01 to about 100µM.

The molecules active on group 1 mGluRs were then tested for their potentiation of the release of transmitter from slices of cortex and the molecules active on group 2 were tested for their inhibition of the release of transmitter from slices of rat stria. The methods used for the experiments reported above are described in: Lombardi et al. *British J. Pharmacol.* 19933, 110, 1407-1412.

The agents of the invention, and in particular compound 44, display selective antagonist activity towards the mGluRs of the second group by antagonizing the effect of L-CCG-1 on the production of cAMP and on the release of transmitter from slices of stria, with an IC_{50} of 10 µM. The effect is selective since the action of

1S, 3R ACDP on phospholipase C is not modified.

Furthermore, the compounds of the invention may act as mGluR-agonists. Agonistic activity can be shown in the following way:

1) Stimulation of phospholipase C in BHK cells which are transfected with mGluRs of group I;

2) Decrease of forskolin-stimulated cAMP-formation in transfected BHK cells expressing one of the mGluRs of class II or III.

The agents of the invention show significant activity in these tests at about 0.01 to about 100µM. Compound 44, for example, acts as an agonist at mGluR4 with an EC50 < 200 µM.

The compounds of the invention are therefore useful in disorders which are linked to metabotropic excitatory amino acid receptors. Such disorders include cerebral ischemia (e.g. due to stroke or cardiac arrest during bypass surgery), head trauma, subarachnoid haemorrage, Alzheimers disease, Huntingtons Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, Parkinson syndrom, convulsive disorders (e.g. epilepsy), muscular spasms, chronic and neuropathic pain, cognitive disorders such as memory deficits, schizophrenia, anxiety, emesis and drug abuse.

For the therapeutic uses envisaged, the compounds of the invention will be formulated in appropriate dosage forms, using conventional techniques and excipients. The dosage will be determined by the doctor in charge, based on the pharmaceutical and pharmacodynamic properties of the compounds. An indicated daily dosage will lie within the range from about 1 mg to about 1g, conveniently administered, for example, in divided doses up to four times a day.

In accordance with the foregoing, the present invention also provides a pharmaceutical composition comprising an agent of the invention, in association with a pharmaceutical carrier or diluent.

The invention furthermore provides an agent of the invention for use as a pharmaceutical, particularly

in disorders linked to metabotropic glutamate receptors, e.g. in the treatment of the above-mentioned disorders.

Mor over the present invention provides the us of an agent of the invention for the manufacture of a medicament for the treatment of the above-mentioned disorders.

In still a further aspect the invention provides a method for the treatment of disorders linked to metabotropic glutamate receptors, e.g. for the above-mentioned disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The examples which follow further illustrate the invention.

Example 1.

(2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)-glycine

a) 6-Phenyl-3-oxabicyclo[3.1.0]hexan-2-one

A solution of cis-3-phenyl-2-propen-1-yl diazoacetate (1 g, 4.95 mmol) in anhydrous toluene (165 ml) was added to a refluxing solution of bis(N-t-butylsalicylaldiminato)copper (II) (0.104 g, 0.25 mmol) in anhydrous toluene (165 ml) with stirring under an argon atmosphere for 12 hours. After cooling, the reaction mixture was evaporated and the residue subjected to flash chromatography, eluting with petroleum ether containing from 10 to 40% of ethyl acetate, to give the title compound. (0.75 g, 87%), m.p. 112-3°C; ^{1}H-NMR ($CDCl_3$) δ 2.60 (2H, m, 1-CH and 5-CH), 2.78 (1H, t, J=8.8 Hz, 6-CH), 4.05 (1H, dd, J=0.6 Hz, J=9.8 Hz, 4-CH_a), 4.35 (1H, dt, J=2.7 Hz, J=9.8 Hz, 4-CH_b), 7.20-7.35 (5H, m, aromatic)

b) 2-Hydroxymethyl-3-phenylcyclopropanecarboxylic acid (4-morpholinyl)amide

A 2.0 M solution of trimethylaluminium in hexane (22.35 ml) was added dropwise over 20 minutes to a solution of morpholine (3.9 ml) in anhydrous CH_2Cl_2

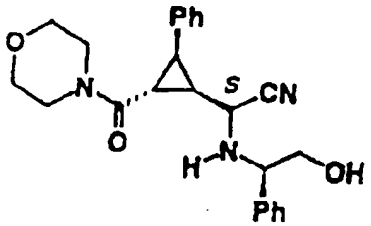
(108 ml) with stirring at room temperature under an argon atmosphere. The stirring was continued for 20 minutes after the addition of a solution of the compound obtained in a) (2.59 g, 14.88 mmol) in anhydrous CH_2Cl_2 (67 ml) over 20 minutes, and the resulting mixture was then heated at 40°C for 20 hours. The reaction mixture was acidified cautiously with 1N HCl, the organic phase was separated out and the aqueous phase was extracted with CH_2Cl_2 (2 x 60 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, the residue (3.7 g) was subjected to flash chromatography, eluting with CH_2Cl_2/methanol (95/5) to give the title compound. (3.50 g, 90%), m.p. 103°C; ^{1}H-NMR ($CDCl_3$) δ 2.00 (2H, m, 1-CH and 2-CH), 2.50 (1H, t, J=5.5 Hz, 3-CH), 3.40-3.80 (8H, m, morpholine), 3.90-4.15 (2H, m, CH_2OH), 7.15-7.40 (5H, m, aromatic)

c) A solution of the compound obtained in b) (3.40 g, 13.03 mmol) in anhydrous tetrahydrofuran (200 ml) was added dropwise over 30 minutes to a solution of lithium hexamethyldisilazide, prepared by adding a 1.5 M solution of butyllithium in hexane (26 ml) to a solution of anhydrous hexamethyldisilazane (8.3 ml) in tetrahydrofuran (200 ml). The addition was carried out at room temperature under an argon atmosphere. Stirring was continued for 1 hour, after which the reaction mixture was diluted with saturated NH_4Cl (500 ml) and extracted with CH_2Cl_2 (3 x 200 ml). The combined organic extracts were then dried (Na_2SO_4) and evaporated to give a residue which was subjected to flash chromatography, eluting with CH_2Cl_2/methanol (95/5) to give the epimer of the compound obtained in b). (3.00 g, 88%); ^{1}H-NMR ($CDCl_3$) δ 2.05 (2H, m, 2-CH and OH), 2.25 (1H, t, J=5.0 Hz, 1-CH), 2.85 (1H, dd, J=5.0 Hz, J=12.0 Hz, 3-CH), 3.50-3.90 (8H, m, morpholine ring), 3.85 (2H, dd, J=6.7 Hz, J=12.0 Hz, CH_2OH), 7.15-7.40 (5H, m, aromatic).

d) 2-Formyl-3-phenylcyclopropanecarboxylic acid (4-morpholinyl)amide

PCC (4.20 g, 19.48 mmol) was added to a solution of the compound obtained in c) (3.00 g, 11.49 mmol) in anhydrous CH_2Cl_2 (130 ml) and the resulting mixture was stirred at room temperature under an argon atmosphere for 16 hours. The reaction mixture was then diluted with ethyl ether and filtered and the solvent was evaporated off. Flash chromatography of the residue and elution with ethyl acetate/petroleum ether (8/2) gave the title compound. (1.90 g, 64%), m.p. 89°C; ^{1}H-NMR ($CDCl_3$) δ 2.78-2.90 (1H, m, 2-CH), 3.12 (1H, t, J=4.9 Hz, 1-CH), 3.35 (1H, dd, J=6.4 Hz, J=9.4 Hz, 3-CH), 6.60-3.90 (8H), m, morpholine ring, 7.18-7.40 (5H, m, aromatic), 9.20 (1H, d, J=5.1 Hz, CHO).

e) R-Phenylglycine (0.45 g, 3.28 mmol) was added to a solution of the aldehyde (0.85 g, 3.28 mmol) in methanol (32.8 ml) and the resulting mixture was stirred at room temperature for 2 hours. After cooling to 0°C, TMSCN (0.65 g, 6.56 mmol) was added and the resulting mixture was stirred for 12 hours at room temperature. Evaporation of the solvent gave a residue which was subjected to medium-pressure chromatography, eluting with CH_2Cl_2/methanol (98/2) to give the compound of formula:

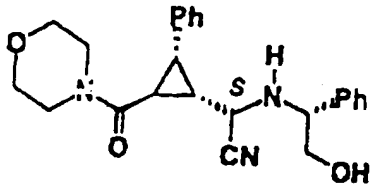


(III)

(3.00 g, 2%), m.p. 123-4°C ^{1}H-NMR ($CDCl_3$) δ 2.20 (2H, m, CHCO and CH-CHN), 2.80 (1H, d, J=9.6 Hz, CHCN), 3.10 (2H, m, CHPh and OH), 3.40-3.90 (10H, m, morpholine and CH_2OH), 3.95 (1H, dd, J=3.8 and 13.5 Hz, $CH-CH_2OH$), 6.70-7.40 (10H, 2 x m, aromatic).

Subsequent elution with the same solvent gave the

compound of formula



(IV)

(0.450 g, 33%), m.p. 146-7°C; ^{1}H-NMR ($CDCl_3$) δ 2.25 (2H, m, CHCO and CH-CHN), 2.60 (1H, d, J=8.0 Hz, CHCN), 2.90 (2H, m, CHPh and OH), 3.50-4.00 (11H, m, morpholine, CH_2OH and CH-CH_2OH), 6.90-7.40 (10H, 2 x m, aromatic).

f) (2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)glycine

Lead tetraacetate (0.360 g, 0.81 mmol) was added to a solution of the compound obtained in e), formula (IV) (0.300 g, 0.74 mmol) in an anhydrous methanol/methylene chloride mixture (12 ml, 1/1); after 10 minutes, water (10 ml) was added and the resulting mixture was filtered through Celite. After evaporation of the solvent, the residue was refluxed in 6N HCl (30 ml) for 12 hours. The reaction mixture was washed with CH_2Cl_2 (2 x 10 ml) and evaporated. The residue was subjected to chromatography on an ion exchange resin of Dowex 50 x 2 200 type: elution with 10% pyridine gave the title compound. (0.110 g, 63%), m.p. 221°C; ^{1}H-NMR (D_2O+DCl) δ 215 (1H, td, J=5.2 and 9.3 Hz, 1'-CH), 2.50' (1H, t, J=5.2 Hz, 2'-CH), 3.05 (1H, dd, J=5.2 and 9.3 Hz, 3'-CH), 3.20 (1H, d, J=10.2 Hz, 2-CH), 7.30 (5H, br s, aromatic); ^{13}C-NMR (D_2O+DCl δ 22.90 (C-1'), 27.76 (C-2'), 31.33 (C-3') 51.50 (C-2), 127.66, 128.57), 128.57, 128.94, 133.26 (aromatic), 169.69, 175.27 (CO); $[\alpha]_D^{20}$-108 (c 0.15, 2.5N HCl).

Example 2

In a similar manner to Example 1, starting with the appropriate aldehydes of formula (II) and using, depending on the case, R- or S-α-phenylglycinol as

indicated in the above schemes 1-4, the following compounds were obtained:

(2R,1'S,2'S,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 86% yield; m.p. 240-1°C; ^{1}H-NMR (D_2O) δ 1.95 (1H, td, J=5.4, 8.9 and 10.8 Hz, 1'-CH), 2.55 (1H, t, J=5.4 Hz, 2'-CH), 2.85 (1H, dd, J=5.4 and 8.9 Hz, 3'-CH), 3.00 (1H, d, J=10.8 Hz, 2-CH), 7.20-7.35 (5H, m, aromatic); ^{13}C-NMR (D_2O+DCl) δ 23.90, 27.78, 29.97, 50.40, 128.03, 128.43, 129, 17, 132.76, 170.81, 175.24; $[\alpha]_D^{20}$ -74 (c 0.30, 2.5N HCl).

(2R,1'R,2'R,3'S). 2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 74% yield; m.p. 221-3°C; ^{1}H-NMR (D_2O) δ 2.10 (1H, dt, J=5.0 and 10.5 Hz, 1'-CH), 2.40 (1H, t, J=5.0 Hz, 2'-CH), 3.00 (2H, m, 3'-CH and 2-CH), 7.30 (5H, d, aromatic); ^{13}C-NMR (D_2O+DCl) δ 22.91, 27.83, 31.39, 51.49, 127.69, 128.59, 128.96, 133.28, 169.70, 175.25; $[\alpha]_D^{20}$ +100 (c 0.20, 2.5N HCl).

(2S,1'R,2'R,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 70% yield; $[\alpha]_D^{20}$ +72 (c 0.30, 2.5N HCl).

(2R,1'R,2'S,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; Dowex 50WX2-200 (10% pyridine); 48% yield; m.p. 219-220°C; ^{1}H-NMR (D_2O) δ 1.80 (1H, dt, J=9.4 and 11.9 Hz, 1'-CH), 2.49 (1H, t, J=9.4 Hz, 2'-CH), 2.75 (1H, t, J=9.4 Hz, 3'-CH), 4.10 (1H, d, J=11.9 Hz, 2-CH), 7.10-7.30 (5H, m, aromatic); ^{13}C-NMR (D_2O+DCl) δ 23.99, 24.54, 28.51, 49.00, 127.86, 129.20, 129.71, 133.33, 171.27, 175.24; $[\alpha]_D^{20}$ +20 (c 0.50, 2.5N HCl).

(2R,1'S,2'R,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glcyine; Dowex 50WX2-200 (10% pyridine); 53% yield; m.p. 219-220°C; ^{1}H-NMR (D_2O) δ 1.90 (1H, dt, J=8.8 and 11.5 Hz, 1'-CH), 2.55 (1H, t, J=8.8 Hz, 2'-CH), 2.80 (1H, t, J=8.8 Hz, 3'-CH), 4.15 (1H, d, J=11.5 Hz, 2-CH), 7.10-7.30 (5H, m, aromatic); ^{13}C-NMR (D_2O+DCl) δ 23.46, 24.20, 28.54, 49.16, 127.61, 128.95, 129.49, 132.94, 171.05, 173.98; $[\alpha]_D^{20}$ -17 (c 0.60, 2.5N HCl).

(2S,1'S,2'R,3'R)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 48% yield; $[\alpha]_D^{20}$-21 (c 0.50, 2.5N HCl).

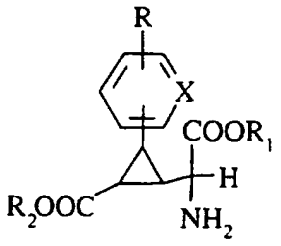
(2S,1'R,2'S,3'S)-2-(2'-Carboxy-3'-phenylcyclopropyl)-glycine; 55% yield; $[\alpha]_D^{20}$ +18 (c 0.40, 2.5N HCl).

(2S,1'S,2'S,3'R)-2-(2'-Carboxy-3'-o-methoxyphenyl-cyclopropyl)glycine.

(0.100 g, 82%), m.p. 219-20°C; ^{1}H-NMR (D_2O+DCl) δ 2.15 (1H, td, J=5.8 and 10.3 Hz, 1'-CH), 2.40 (1H, t, J=5.8 Hz, 2'-CH), 2.9-3.10 (2H, m, 3'-CH and 2-CH), 3.80 (3H, s, OMe), 6.90-7.40 (4H, m, aromatic); $[\alpha]_D^{20}$ -81 (c 0.15, 2.5N HCl).

CLAIMS

1. A compound of formula I



(I)

wherein

R is hydrogen, halogen selected from chlorine,bromine, fluorine or iodine, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4-haloalkoxy, cyano, nitro, -$COOR_1$ (R_1 being as defined below), -$CONR_3R_4$ (R_3 and R_4 independently being hydrogen or C_1-C_4alkyl), -$PO(OR_1)_2$ (R_1 being as defined below), -SO_3R_1 (R_1 being as defined below) or -NH-CO-R_5 (R_5 being C_1-C_4alkyl or phenyl), R_1 and R_2, independently, are hydrogen, C_1-C_4alkyl or benzyl, and

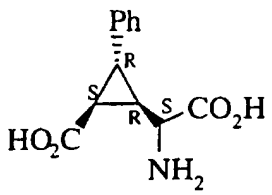
X is =CH-, =N- or $=N^{+}(O^{-})-$

or a salt thereof.

2. A compound of formula I according to claim 1 wherein R is hydrogen, an halogen selected from chlorine, bromine, fluorine or iodine, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl or C_1-C_4haloalkoxy, R_1 and R_2 are hydrogen and X is =CH- or =N- in ortho position to the bond which is linked to the cyclopropyl moiety, or a salt thereof.

3. A compound of claim 1 wherein R is hydrogen or C_1-C_4alkyl, R_1 and R_2 are hydrogen and X is =CH-.

4. The compound of formula



and its salts.

5. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use as a pharmaceutical.

6. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use in disorders linked to metabotropic glutamate receptors.

7. A compound of anyone of claims 1 to 4, in free or pharmaceutically acceptable salt form, for use in the treatment of cerebral ischemia, head trauma, subarachnoid haemorrage, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, Parkinson syndrome, convulsive disorders, muscular spasms, pain, cognitive disorders, schizophrenia, anxiety, emesis and drug abuse.

8. A pharmaceutical composition comprising a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent.

9. The use of a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, as a pharmaceutical for the treatment of disorders linked to metabotropic glutamate receptors.

10. The use of a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form, for the manufacture of a medicament for the treatment of disorders linked to metabotropic glutamate receptors.

11. A method for the treatment of disorders linked to metabotropic glutamate receptors in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of anyone of claims 1 to 4 in free or pharmaceutically acceptable salt form.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 96/05079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/48 A61K31/195 C07D213/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BIOORG. MED. CHEM. LETT. (1996), 6(18), 2243-2246 CODEN: BMCLE8;ISSN: 0960-894X, 1996, XP000617002 MARINOZZI, MAURA ET AL: "Asymmetric synthesis of enantiomerically pure (2S,1'S,2'S,3'R)-phenylcarboxycyclopropylglycine (PCCG-4): a potent and selective ligand at group II metabotropic glutamate receptors" see the whole document --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 1997	10.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Sánchez García, J.M.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 96/05079

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4959493	25-09-90	CA-A-	1305177	14-07-92
		JP-A-	1093563	12-04-89
		JP-B-	7068192	26-07-95
WO-A-9308158	29-04-93	AT-T-	137215	15-05-96
		DE-D-	69210214	30-05-96
		DE-T-	69210214	02-10-96
		EP-A-	0564658	13-10-93
		JP-T-	6504553	26-05-94
		US-A-	5334757	02-08-94
EP-A-0363994	18-04-90	JP-A-	2108654	20-04-90
		DE-D-	68909362	28-10-93
		DE-T-	68909362	10-03-94
		ES-T-	2059669	16-11-94
		US-A-	5068412	26-11-91